Citation:

Quinlivan EP, Gregory JF 3rd. Re-assessing folic acid consumption patterns in the United States (1999 to 2004): Potential effect on neural tube defects and overexposure to folate. *Am J Clin Nutr*. 2007 Dec; 86 (6): 1,773-1,779.

PubMed ID: 18065598

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To quantify changes in folate intake after folic acid fortification and to quantify the effect the change in consumption had on the incidence of neural tube defects (NTDs).

Inclusion Criteria:

- Data from national Health and Nutrition Examination Survey (NHANES)1988 to 2004
- Also, 11 intervention studies were used to determine the relationship between chronic folate intervention and changes in steady state serum folate concentrations. Intervention periods were sufficient to achieve plateau serum folate concentrations and daily folate intervention was expressed as daily folate equivalents (DFEs).

Exclusion Criteria:

A study by van Oort et al was excluded. After regressing folate intake and change in serum or plasma folate and determining the slope of the regression line, the authors compared the slope from this regression line to the slope derived from their previous publication and with that of van Oort. The slope of the regression line from van Oort et al was determined by a coincidence test to be significantly different from the slope defined by the other data points (the author's previously published work and this current data set).

Description of Study Protocol:

Recruitment

Pre-fortification and post-fortification serum and red blood cell (RBC) folate concentrations for women of childbearing age were determined from NHANES studies (1999 to 2004).

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- The study calculated the change in serum folate concentration (serum folate data from each of the NHANES post-fortification surveys (1989 to 1994 NHANES III) and used reverse prediction to compare the changes in serum folate concentrations with the linear regression equation derived above. Finally, they calculated the apparent change in daily folate consumption since fortification
- Risk for NTD for each NHANES survey was calculated based on an equation by Daly et al. which defined the relationship between RBC folate concentrations and NTD risk. NTD risk was expressed relative to the median pre-fortification group.

Data Collection Summary:

Timing of Measurements

Data were from NHANES surveys 1989 to 2004.

Dependent Variables

Risk for NTD: Calculated based on an equation by Daly et al. which defined the relationship between RBC folate concentrations and NTD risk. NTD risk was expressed relative to the median pre-fortification group.

Independent Variables

- Change in serum folate concentration (serum folate data from each of the NHANES post-fortification surveys-serum folate data from 1989 to 1994 NHANES III
- Apparent total daily folate consumption based on total serum folate concentration.

Control Variables

Not applicable.

Description of Actual Data Sample:

- *Initial N:* 1,032
- *Attrition:* 777 (after subjects from van Oort's studies were excluded)
- *Age:* Information not available
- *Ethnicity:* Information not available
- *Anthropometrics:* Information not available
- *Location:* United States.

Change in Serum or Plasma Folate Concentrations Observed in Intervention Studies on the Effect of Oral Folic Acid Consumption[1]

Study Group	Male Subjects (percentage)	Dose[2] (mcg per day)	DFE Dose[3] (mcg per day)	Subjects (N)	Change in Folate Concentrations[4]	Data Excluded from Final Analysis
van Oort et al	NS	49	83	42	1.9	yes
van Oort et al	NS	99	168	41	3.2	yes
Venn et al	57	100	170	53	2.4	no
Venn et al	62	100	170	52	2.3	no
Ward et al	100	100	170	30	2.1	no
Melse-Boonstra et al	NS	145	247	54	4.9	no
van Oort et al	NS	198	337	43	5.4	yes
Lamers et al	0	200	340	32	5.8	no
Schorah et al	52	200	340	33	5.1	no
Schorah et al	58	200	340	31	6.0	no
Wald et al	83	200	340	25	4.5	no
PACIFIC study	82	200	340	68	4.9	no
Ward et al	100	200	340	30	4.6	no
Riddell et al	62	298	507	16	4.9	no
Carrero et al	100	340	578	30	6.0	no
Ashfield-Watt et al	42	352	598	108	6.5	no
Ward et al	100	400	680	30	11.0	no
Lamers et al	0	400	680	34	10.0	no
Lamers et al	0	400	680	35	9.8	no
Wald et al	83	400	680	25	11.5	no
van Oort et al	NR	408	694	43	13.0	yes

Riddell et al	62	437	743	16	11.9	no
Wald et al	83	600	1,020	25	13.9	no
van Oort et al	NS	633	1,076	43	18.8	yes
Wald et al	83	800	1,360	25	20.3	no
van Oort et al	NS	872	1,482	43	27.3	yes
Wald et al	83	1,000	1,700	25	24.4	no

1 Studies listed more than once reported the results of multiple interventions. DFE, daily folate equivalent; NS, not stated; 5-CH3-THF, 5-methyltetrahydrofolate.

2 Amount of additional folic acid consumed daily by subjects.

3 Folate and 5-CH3-THF (adjusted for differences in molecular mass) dose multiplied by 1.7, to adjust for their greater bioavailability than that of dietary folate.

4 Change in median or mean serum or plasma folate concentrations after intervention.

Summary of Results:

- In the relation between changes in folate consumption and changes in serum folate concentration, the slope of the data from the studies was linear ($r=0.979$, $P<0.001$). Comparing the data points from the authors previously published study with data from this study, they found no significant ($P>0.6$) difference in slope between the two sets of data. The age of the subjects in the intervention studies had no significant effect on serum folate response
- Both RBC and serum folate concentrations increased between 1988 to 1994 and 1999 to 2000 and then they decreased each year from 1999 to 2000 to 2003 to 2004. Between 1988 to 1994 and 1999 to 2000, the percentage increase in serum and RBC folate concentration was smallest in the women with the highest folate status. The percentage decline in serum and RBC folate concentrations between 1999 to 2000 and 2003 to 2004 was greatest in the women with the highest folate status
- Median folate consumption increased by 529mcg DFE per day between 1988 and 1994 (before fortification) and 1999 to 2000 (after fortification); then decreased by 135mcg DFE per day between 1999 to 2000 and 2003 to 2004. The overall decrease in folate consumption was primarily due to changes in subjects with the highest folate status
- Total folate consumption increased in the year after mandatory fortification (1999 to 2000). However by 2003 to 2004, total folate consumed by subjects in the 90th percentile had decreased to 1,249mcg DFE per day
- The analysis predicted a 43% decrease in NTD risk between 1988 to 1994 and 1999 to 2000. However, it also predicted that NTD risk increased by 4 to 7% between 1999 to 2000 and 2003 to 2004 (calculated by subtracting the relative NTD risk in 1999 to 2000 from that in 2003 to 2004).

	Percentile of Serum Folate Concentration				
	10	25	50	75	90
Serum folate (ng/ml)[1]					
1988-1994	92	119	160	222	296
1999-2000	164	200	255	329	409
2001-2002	163	208	260	318	395
2003-2004	155	188	235	298	367
Change in RBC folate concentration from 1994 (%)					
1988-1994	100[2]	100[2]	100[2]	100[2]	100[2]
1999-2000	180	171	164	155	146
Change in RBC folate concentration from 1999 (%)					
1999-2000	100[2]	100[2]	100[2]	100[2]	100[2]
2001-2002	99	104	102	97	97
2003-2004	95	94	92	91	90

TABLE 2. Change in red blood cell (RBC) folate concentrations between the third National Health and Nutrition Examination Survey (NHANES III) and the annual NHANES surveys from 1999 through 2004

	Percentile of Red Blood Cell Folate Concentration				
	10	25	50	75	90
RBC folate (ng/ml)[1]					
1988–1994	92	119	160	222	296
1999–2000	164	200	255	329	409
2001–2002	163	208	260	318	395
2003–2004	155	188	235	298	367
Change in RBC folate concentration from 1994 (%)					
1988–1994	100[2]	100[2]	100[2]	100[2]	100[2]
1999–2000	180	171	164	155	146
Change in RBC folate concentration from 1999 (%)					
1999–2000	100[2]	100[2]	100[2]	100[2]	100[2]
2001–2002	99	104	102	97	97
2003–2004	95	94	92	91	90

1 Values for 1988 to 1994 are from Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race or ethnicity; United States, 1999 to 2000. *MMWR Morb Mortal Wkly Rep.* 2002; 51: 808-810. Values for 1999 to 2000, 2001 to 2002 and 2003 to 2004 are from Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race or ethnicity; United States, 1999 to 2000, 2001 to 2002 and 2003 to 2004. *MMWR Morb Mortal Wkly Rep*. 2007; 55: 1,377-1,380.

2 Reference group.

TABLE 3. Change in serum folate concentrations between the third National Health and Nutrition Examination Survey (NHANES III) and the annual NHANES surveys from 1999 through 2004

	Percentile of Serum Folate Concentration				
	10	**25**	**50**	**75**	**90**
Serum folate (ng/ml)*1*					
1988–1994	2.3	3.1	4.8	7.8	11.7
1999–2000	6.3	8.9	12.6	17.3	24.7
2001–2002	6.4	8.5	11.4	15.2	19.7
2003–2004	6.0	7.8	10.6	14.1	18.5
Change in serum folate from 1988–1994 (ng/ml)*2*					
1999–2000	4.0	5.8	7.8	9.5	13.0
2001–2002	4.1	5.4	6.6	7.4	8.0
2003–2004	3.7	4.7	5.8	6.3	6.8
Change in serum folate concentration from 1994 (%)					
1988–1994	100[3]	100[3]	100[3]	100[3]	100[3]
1999–2000	274	287	263	222	211
Change in serum folate concentration from 1999 (%)					
1999–2000	100[3]	100[3]	100[3]	100[3]	100[3]
2001–2002	102	96	90	88	80
2003–2004	95	88	84	82	75

1 Values for 1988-1994 are from Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race or ethnicity; United States, 1999 to 2000. *MMWR Morb Mortal Wkly Rep.* 2002; 51: 808-810. Values for 1999 to 2000, 2001 to 2002 and 2003 to 2004 are

from Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race or ethnicity; United States, 1999 to 2000, 2001 to 2002 and 2003 to 2004. *MMWR Morb Mortal Wkly Rep.* 2007; 55: 1,377-1,380.

2 Calculated by subtracting the NHANES III concentrations from the concentration in each of the annual NHANES surveys.

3 Reference group.

TABLE 4. Change in daily folate intake between the third National Health and Nutrition Examination Survey (NHANES III) and the annual NHANES surveys from 1999 through 2004 and total daily folate intake in each study year, stratified by percentile of serum folate concentration*1*

	Percentile of Serum Folate Concentration				
	10	**25**	**50**	**75**	**90**
Change in folate intake from 1988–1994 (mcg DFE per day)*2*					
1999-2000	273	394	529	643	879
2001-2002	280	368	448	502	542
2003-2004	253	320	394	428	462
Total folate consumed (mcg DFE per day)*3*					
1988-1994	159	213	327	529	791
1999-2000	428	603	852	1,168	1,666
2001-2002	435	576	771	1,027	1,329
2003-2004	408	529	717	953	1,249

1 DFE, daily folate equivalents.

2 Calculated from the change in serum folate concentration between NHANES III and the annual NHANES surveys from 1999 through 2004 by using a regression equation relating changes in serum folate concentration to changes in daily folate intake where y=0.0145x+0.132; r=0.979, P<0.0001.

3 Calculated from the total serum folate concentrations in NHANES III and the annual NHANES surveys from 1999 through 2004 by using a regression equation relating changes in serum folate concentration to changes in daily folate intake y=0.0145x+0.132; r=0.979, P<0.0001.

TABLE 5. Relative risk of having a child with a neural tube defect (NTD) by percentile of

red blood cell folate concentration during the third National Health and Nutrition Examination Survey (NHANES III) and each of the annual NHANES surveys from 1999 through 2004*1*

	Percentile of Red Blood Cell Folate Concentration				
	10	**25**	**50**	**75**	**90**
Relative NTD risk vs. pre-fortification median (%)					
1988-1994	196	143	100[2]	67	47
1999-2000	97	76	57	42	32
2001-2002	98	73	55	43	33
2003-2004	104	82	63	47	36

1 RCF, red (blood) cell folate. The risk was estimated by fitting red blood cell concentrations into an equation from Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race or ethnicity; United States, 1999 to 2000. *MMWR Morb Mortal Wkly Rep.* 2002; 51: 808-810. NTD risk = $\exp^{(0.6489-1.2193 \times \ln[\text{RCF (mg/L)}])}$.

2 Reference group.

Author Conclusion:

- Recent decrease in serum and RBC folate concentrations in the US is due to changes among women who were consuming the highest amount of folate, which would reduce risk associated with folate over-consumption
- This coincides with their estimated NTD occurrence since the estimated occurrence would have been greater if there was a true decrease in folate concentrations
- Continued monitoring of food intake is needed to increase folate among those with low concentrations and limit intake among those with high concentrations
- Folate intake among men should be determined before making changes to uniform fortification programs.

Reviewer Comments:

Authors note that other factors may have affected folate status including change in folic acid supplements, change in diets low in enriched grain products (low carbohydrate diets) and consumption of fortified products.

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	???
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	???
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	???
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes